

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

*Part #38*

Applicant: Timothy J. Barberich and James W. Young

Applicant's Docket No.: SPC89-05      Group Art Unit: 1205

Filed: December 7, 1993

Examiner: R. Henley III

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY  
PURE R(-) ALBUTEROL

DECLARATION UNDER 37 C.F.R. §1.132

To: Hon. Commissioner of Patents and Trademarks  
Washington, D.C. 20231

Dear Sir:

I, T. Scott Johnson, declare:

1. I reside at 415 Nashwatic Road, Concord, Massachusetts.
2. I earned a Bachelor of Science degree from the University of Alabama in 1969 and an M.D. degree from the University of Alabama School of Medicine in 1973. I am certified by the American Board of Internal Medicine with a subspecialty in Pulmonary Disease. I have been a Clinical and Research Fellow in Pulmonary Disease at the University of Colorado Medical Center, and, until 1991 I was Assistant Professor of Medicine at Harvard Medical School, where I was an Attending Consultant in Pulmonary Disease.
3. I am the author of 16 original articles, 8 review articles and a textbook on subjects relating to pulmonary disease.
4. I am presently a Managing Partner of Medical Portfolio Management, Inc., in Cambridge, Massachusetts. In this capacity, I have been retained by Sepracor, Inc.

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(assignee of the above-identified application) as a paid consultant on an hourly basis. My compensation from Sepracor is unaffected by any change in status of the above-identified application, and I will not benefit financially from issuance of a patent thereon.

5. I have reviewed and do understand the contents of the above-identified application, which is directed to a method for treating asthma while avoiding the side effects associated with racemic albuterol by using the pure R-enantiomer of albuterol. As a result of my knowledge and experience I make the following observation:

The term "chronic" does not appear in the specification. However, the concept of chronic administration is implicit in the description of modes of administration that is found in the specification. In particular, on page 4 in the paragraph extending from line 4 to line 13, the concepts of the two modes of therapy (acute and chronic) are discussed. In the first mode (acute) the albuterol is administered "after onset of asthma". In the second, albuterol is administered "prophylactically, that is, before the bronchospasm [sic] begins in an asthma attack, to prevent its occurrence.."

Asthma is defined (Webster's Medical Desk Dictionary, 1986 edition) as "a condition often of allergic origin that is marked by continuous or paroxysmal labored breathing accompanied by wheezing, by a sense of constriction in the chest, and often by attacks of coughing or gasping". To be noted is the distinction between asthma (a condition or disease state) and an asthmatic attack (an acute episode of coughing, wheezing or gasping), which often accompanies the general disease state. Asthmatic attacks can be treated acutely; asthma is treated chronically.

Albuterol is, in the presently claimed invention, intended to be administered to "an individual who has asthma" (line 5 to 6). Since the patient has asthma (i.e. suffers from a disease state), and treatment is to be prophylactic, treatment would have to be chronic. If the treatment were not chronic, cessation of administration might or might not lead to an immediate attack, but it would certainly lead to

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reestablishment of the disease condition.

Thus, although the term "chronic" is not used, its implication is clear in the description of prophylactic therapy. Indeed, since one is commonly not able to predict the onset of an acute attack, and since current practice in the treatment of asthma favors the treatment of the underlying disease state, many patients are treated chronically. Thus the person of skill in the art would understand that the application was referring to chronic therapy when it speaks of either prophylactic or periodic administration.

That the concept of chronic medication is envisioned is further supported by the disclosure on page 5, line 6 to line 9, regarding oral therapy. An oral regimen of "1 to about 8 mg two to four times daily" would not make sense as acute therapy.

6. I further declare that all statements of the foregoing declaration made of my own knowledge are true and that all statements made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issuing thereon.

Signed by me this 11<sup>th</sup> day of May, 1994.

  
T. Scott Johnson

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May 11, 1994

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PHILIP E. HANSEN, PH.D.  
PATENT AGENT

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Date: May 12, 1994

From: Philip E. Hansen

Heslin & Rothenberg, P.C.  
Fax No.: (518) 452-5579

No. of Pages: 2 (Including this Cover Sheet)

Re: Our Ref.: 0701.027B

To: Examiner Raymond J. Henley, III (Group Art Unit 1205)

Fax No.: 1-703-308-4556

Message: \_\_\_\_\_  
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Date: July 13, 1994

From: Philip E. Hansen

Heslin & Rothenberg, P.C.  
Fax No.: (518) 452-5579

No. of Pages: 5 (Including this Cover Sheet)

Re: Our Ref. 0701.027B

To: Examiner Raymond J. Henley, III (Group Art Unit 1205)

Fax No.: 1-703-308-4556

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Art Unit 121

Paper No. 22

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Appeal No. 629-61

JAN 28 1987

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HEARD:  
November 24, 1986

PAT. & T.M. OFFICE  
BOARD OF PATENT APPEALS  
AND INTERFERENCES

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

Ex parte Giorgio Ferrari  
and  
Vittorio Vecchiatti

Application for Patent filed October 14, 1982, Serial No. 434,362; a Continuation-in-Part of Serial No. 371,428 filed April 23, 1982; a Continuation of Serial No. 123,770 filed February 20, 1980, Abandoned. Process for the Separation of the Two Optical Isomers of Moprolol and Pharmaceutical Compositions of the Laevorotatory Antipode Thereof.

Arthur R. Crawford et al. for appellants.

Primary Examiner - Richard A. Schwartz.

Before Milestone, Goldstein and Downey, Examiners-in-Chief.  
Milestone, Examiner-in-Chief.

This is an appeal from the final rejection of claims 1 to 3, which are all of the claims in the case.

The claims are reproduced below:

1. A pharmaceutical composition for treating hypertension without causing cardiac depression which comprises a therapeutically effective amount of the laevorotatory form of moprolol or of a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

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2. A method for a long-term treatment of hypertension comprising administering to a hypertensive patient requiring said treatment an effective amount of the laevorotatory form of moprolool or of a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition for treating hypertension without causing cardiac depression which comprises from 5 to 250 mg of the laevorotatory form of moprolool or of a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

The following is the art relied upon by the examiner:

Wilhelm et al. (Wilhelm)	3,483,221	Dec. 9, 1969
Crowther et al. (Crowther)	3,501,769	Mar. 17, 1970
Gilman et al. (Gilman)	3,538,150	Nov. 3, 1970
Ferrari	3,911,136	Oct. 7, 1975

Ferrini et al. (Ferrini), Arzneim-Forsch, 20(8), 1970, pp. 1074-1079.

Burger (Ed.), Medical Chemistry (New York, Interscience, 1970), 3rd Ed., pp. 1052-1055.

The appealed claims have been rejected under 35 U.S.C. 103 as unpatentable over Crowther, Ferrini and Ferrari considered with Wilhelm, Gilman and Burger. We will not sustain the rejection.

The invention is directed to pharmaceutical compositions containing the levo form of moprolool (1-(o-methoxyphenoxy)-3-isopropylamino-2-propanol) and its use in treating hypertension.

The racemic moprolool being known for the treatment of hypertension by virtue of its  $\beta$ -blocking activity, the knowledge that the levo form would have been expected to be more active and the resolution of the racemic mixture being within the skill of the art and obvious within the meaning of 35 U.S.C. 103 (Appeal No. 591-61, decided August 16, 1985), the claimed compositions and their method of use would have been clearly prima facie obvious.

It is appellants' position that not only does the levo isomer possess double the activity of the racemic mixture (dextro isomer being essentially inactive), the levo isomer also possesses a cardiac stimulant action while the dextro form as well as race-

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mic mixture possesses cardiac depressant action. Appellants argue that one would not have expected one of the isomers to possess cardiac stimulant activity while the other, depressant activity. A declaration has been submitted in support of appellant's position.

The examiner, on the other hand, argues that the reduction of the cardiac depressant activity would have been predictably enhanced in the levo form, there being a fine line of difference between enhanced reduction of depressant activity and mild stimulation of said activity. The examiner contends that as the dextro isomer is clearly exerting a negative effect on the racemic mixture; once the racemic mixture is free from the dextro form, observation of the opposite effect (i.e., cardiac stimulant effect) would not have been surprising.

We find the examiner's position is not supported by the evidence of record. Although Ferrini indicates that the myocardial depressant effect of moprolool is about seven times less than that of propranolol, there is no evidence or reason to believe that the levo form, while being a more active hypertensive agent, would possess a cardiac stimulant effect. It does not necessarily follow that a reduction in depressant effect would necessarily result in a stimulant effect. Thus, while one might expect that the levo form would have a reduced depressant effect, there would be no reason to believe that a reduction in the depressant effect would necessarily result in the opposite stimulant effect. While it would appear from the Burger reference that all known  $\beta$ -blockers used in the treatment of hypertension have either a cardiac depressant effect or no effect, nowhere is it seen in the evidence presented that a cardiac stimulant effect had ever been observed or recognized. While the cardiac depressant effect of  $\beta$ -blockers may be desirable in the treatment of certain types of hypertension, the Ferrari declaration indica-

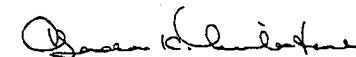



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tes that in the treatment of certain types of hypertensive patients there is a need for  $\beta$ -blockers which, as here, possess cardiac stimulant activity. Accordingly, since it would not have been expected that  $\beta$ -blockers of the type involved herein would possess cardiac stimulant activity rather than depressive activity and as there is a particular need in the treatment of specific hypertensive patients with  $\beta$ -blockers with such properties, the prima facie case of obviousness has been rebutted.

In view of the foregoing, the decision of the examiner in rejecting the claims is reversed.

REVERSED

  
Gordon K. Milestone  
Examiner-in-Chief

  
Melvin Goldstein  
Examiner-in-Chief

  
Mary R. Downey  
Examiner-in-Chief

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